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(71) Applicant *(for all designated States except US)*: NEWTEC V.P. LIMITED [GB/GB]; 2 Newtech Square, Deeside Industry Park, Clwyd, Wales CH5 2NT (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : CHARLESWORTH, David [GB/GB]; Ollerton Lodge, School Lane, Ollerton, Knutsford, Cheshire WA16 8SD (GB). UNDERWOOD, Christopher, John [GB/GB]; 22 Keswick Avenue, Denton, Manchester M34 3QD (GB). CHIAN, Kerm, Sin [MY/GB]; 22 Fulbrook Road, Bevington, Spital, Wirral L63 9HT (GB).

(74) Agents: McNEIGHT, David, Leslie et al.; McNeight & Lawrence, Regent House, Heaton Lane, Stockport, Cheshire SK4 1BS (GB).

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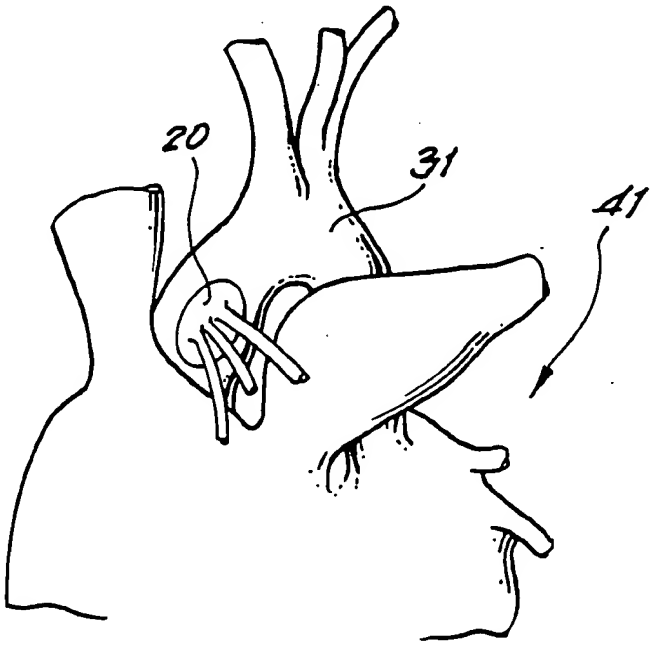
(54) Title: POLYMER PRODUCTS



(57) Abstract

A polymer product for use e.g. as vascular prosthesis is formed from a luminate vessel by precipitating on to said vessel a sheet of polymer from a solution comprising an organic solvent and precipitable polymer and forming an aperture in said sheet, said aperture communicating with the lumen of said vessel.

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POLYMER PRODUCTS

This invention relates to methods for making polymer products and to novel products made according to the methods.

Polymer products in the form of vascular prostheses conventionally comprise a conduit having varying dimensions and mechanical characteristics which are as close as materials and manufacturing processes will allow to the vessel in the body whose function it is intended that the prosthesis should replace.

A number of tubular prostheses may be grafted into a single vascular system.

There is merit, at least conceptually, in attempting to maintain as much as possible of the host vascular tissue during surgical procedures which involve vascular replacement, principally because there is less alien material introduced into the patient.

Polymer products which comprise a branch and arms emanating therefrom may typically be produced by joining the arms to an independently fabricted branch region. Whilst this procedure has the advantage that it allows the construction of relatively complex branched

structures, disadvantages include the product lacking a relatively uniform mechanical consistency; together with a relatively time consuming and thus expensive preparative procedure.

Where a vascular system branches, tubular prostheses may be grafted onto each of the arms comprised thereby. This technique suffers from the serious disadvantage in that it necessitates joins at the increased number of junctions between host and prosthetic vascular material. Consequently, the time spent by the patient under anaesthetic and subject to cardiopulmonary bypass is increased which increases the likelihood of the development of pulmonary and circulatory system disorders, together with the raised possiblilty of cardiac ischaemia, necrosis and infarct.

Moreover, there is a finite possibility that a prosthesis will fail mechanically at the region of its attachment to host vascular material, conventionally regarded as the weakest and most sensitive region of the graft. An increased number of such attachment regions in a single vascular system synergistically increases the possibility of failure of the prosthetic vascular system as a whole.

The present invention provides inter alia methods of producing vascular products, particularly in

the form of prostheses, which overcome the disadvantages and deficiencies which characterise prior art vascular prosthetic products.

According to the present invention there is provided a method of forming a polymer product from a luminate vessel, comprising precipitating onto said vessel a sheet of polymer from a solution comprising an organic solvent and precipitable polymer and forming an aperture in said sheet, said aperture communicating with the lumen of said vessel.

The invention further includes a method of forming a polymer product comprising a luminate vessel and sheet therearound, comprising precipitating onto a product former a layer of polymer from a solution comprising an organic solvent and precipitable polymer.

The invention also includes products made according to the aforementioned methods.

The polymer may comprise between 17 per cent and 30 per cent by weight of the solution comprising said polymer and solvent.

The product may exhibit approximately a 20 per cent shrinkage during the manufacture thereof.

The product may be formed from an existing luminate vessel, itself formed from a solution chemically similar or identical to said solution.

The polymer may be biocompatible and may comprise a vascular prosthesis.

The prosthesis may comprise a graft adapted for use in a part of a vascular system comprising branches therein, such as, for example, that part of the aorta from which the coronary arteries arise.

Said solution may further comprise a porosifier which may be insoluble in said solution but soluble in aqueous systems.

The porosifier may comprise a carbonate, such as, for example, sodium hydrogen carbonate.

Said porosifier may have an average particle size of 50 to 100 microns, and may comprise between 10 and 60 per cent by weight of the solution.

Said solution may further comprise a surfactant.

The surfactant may be an anionic detergent, such as, for example, an alkoxy sulphite.

Said surfactant may be an alkaline metal salt of dodecyl sulphate, such as sodium dodecyl sulphate.

Said surfactant may comprise between 0.1 and 10 per cent by weight of said solution.

The wall thickness of said product may be 0.5 to 1.5 millimetres, and if said product comprises a luminate vessel, the lumenal diameter thereof may be 3 to 30 mm.

The polymer of which said product is comprised may be polyurethane.

Said polyurethane may be a linear segmented poly(ether)urethane with a number average molecular weight in the region of 20 to 100 kDa.

The invention will be further apparent from the following description and several figures of the accompanying drawings, which illustrate, by way of example only, methods of forming polymer products, according to the invention and polymer products made according to the methods.

Of the figures :-

Figure 1 shows a method of producing a polymer vascular prosthesis from a plurality of luminate vessels;

Figure 2 shows a second method of forming a polymer vascular prosthesis according to the invention, in which said prosthesis is precipitated onto the surface of a multi-tubular former;

and Figure 3 shows a polymer product in the form of a vascular prosthesis in situ comprising a region of the aorta from which the coronary arteries arise, together with a region of each of said arteries.

Figures 1 and 2 illustrate methods of forming polymer products in the form of prosthetic grafts adapted for use in a region of a vascular system comprising branches therein.

As shown in Figure 1, the prosthesis 10 is formed from two luminate vessels 11,12 by precipitating thereonto a sheet 13 of polymer from a solution comprising an organic solvent and precipitable polymer. Apertures 14,15 are formed in the sheet 13, so that

there is a fluid communication between the sheet 13 and the lumen of each vessel.

In a second method of forming a vascular prosthesis, the prosthesis 20 comprises a plurality of luminate vessels 21 having a sheet 22 of polymer therearound and is formed by precipitating onto a product former 23 comprising a plurality of tubular conduits 24 a layer of polymer from a solution comprising an organic solvent and precipitable polymer

Figure 2 shows the prosthesis 20 of Figure 2 as a graft in the aorta 31 of a human heart, shown partially at 41.

The polymer can comprise at least 17 per cent but less than 30 per cent by weight of the solution comprising said polymer and solvent and the polymer can exhibit approximately a 20 per cent shrinkage during the precipitation thereof.

Preferably, where the product is formed from an existing luminate vessel, as shown in Figure 1, the solution from which the vessel is formed is chemically similar or identical to the solution comprising organic solvent and precipitable polymer from which solution said sheet is precipitated.

Vascular protheses necessarily should be made from biocompatible material, and the polymer of which said product is comprised is a polyurethane, characterised by being a linear segmented poly(ether)urethane with a number average molecular weight in the region of 20 to 100 kDa.

It is desirable that prostheses for use in the blood vascular system should have pores in their walls, preferably relatively large on the external surface, and relatively small on the luminal surface of the prosthesis.

Such pores enable formation of pseudointima by endothelial cells particularly, but also pericytes and other cells normally found in the vascular architecture. Such cells can present a non-thrombogenic surface to blood flowing through the prosthesis and, additionally, release factors which are ordinarily non-thrombogenic, and platelet anti-aggregators and anti-thrombogenic derivatives of arachidonic acid.

Preferably, the solution from which the prosthesis is precipitated further comprises a porosifier, such as sodium hydrogen carbonate, which is insoluble therein but soluble, for example, in an aqueous system.

Said porosifier has an average particle size of 50 to 100 microns, and comprises between 10 and 60 per cent by weight of the solution.

A surfactant is added to the solution to modulate further the porosity of the walls, particularly at the precipitation surfaces.

Although the surfactant can comprise between 0.1 and 10 per cent by weight of said solution the preferred concentration is about 2 per cent.

The wall thickness of the prosthesis corresponds to the thicknesses of the vessels found in the body and which it is intended that the prosthesis should replace.

Alternatively, a wall thickness of the prosthesis can be determined from an analysis of the physio-mechanical requirements that must be met by the prosthesis, with relatively little regard to the wall thickness thereof.

Typically, the wall thickness of the prosthesis is 0.5 to 1.5 millimetres, and the lumenal diameter thereof is 3 to 30 mm.

Although the present invention has been described in conjunction with particular embodiments, it

will be appreciated by those skilled in the art that various other changes, omissions and additions thereto may be made without departing from its scope as described herein.

For example, the polymer products may comprise bio-compatible sheets having pores, the sheets acting as matrices into which cells may migrate in tissue culture. Such sheets may be of use in skin grafts, for example.

The polymer products may be used as filters and selectively permeable membranes.

CLAIMS

1. A method of forming a polymer product from a luminate vessel, comprising precipitating onto said vessel a sheet of polymer from a solution comprising an organic solvent and precipitable polymer and forming an aperture in said sheet, said aperture communicating with the lumen of said vessel.

2. A method of forming a polymer product comprising a luminate vessel and sheet therearound, comprising precipitating onto a product former a layer of polymer from a solution comprising an organic solvent and precipitable polymer.

3. A method according to claim 1 or claim 2, in which the polymer comprises at least 17 per cent but less than 30 per cent by weight of the solution comprising said polymer and solvent.

4. A method according to any preceding claim, in which during formation of said product there is approximately a 20 per cent shrinkage.

5. A method according to claim 1, in which said solution is chemically similar or identical to the solution comprising an organic solvent and precipitable polymer from which said sheet is precipitated.

6. A method according to any preceding claim, in which the polymer is bio-compatible.

7. A method according to claim 1, in which said solution further comprises a porosifier.

8. A method according to claim 7, in which said porosifier is insoluble in said solution.

9. A method according to claim 8, in which the porosifier is soluble in aqueous systems.

10. A method according to any one of claims 7 to 10, in which the porosifier comprises a carbonate.

11. A method according to claim 10, in which the porosifier is sodium hydrogen carbonate.

12. A method according to any one of claims 7 to 11, in which the porosifier has an average particle size of 50 to 100 microns.

13. A method according to any one of claims 7 to 12, in which the porosifier comprises between 10 and 60 per cent by weight of the solution.

14. A method according to claim 1, in which said solution further comprises a surfactant.

15. A method according to the previous claim, in which the surfactant is an anionic detergent.

16. A method according to claim 15, in which the anionic detergent is an alkoxy sulphite.

17. A method according to any one of claims 14 to 16, in which the surfactant is an alkaline metal salt of dodecyl sulphate.

18. A method according to any one of claims 14 to 17, in which the surfactant is sodium dodecyl sulphate.

19. A method according to any one of claims 14 to 18, in which the surfactant comprises between 0.1 and 10 per cent by weight of said solution.

20. A method according to claim 1 or claim 1, in which the wall thickness of said product is 0.5 to 1.5 millimetres.

21. A method according to claim 1 or claim 2, in which the diameter of the lumen of said vessel is 3 to 30 mm.

22. A method according to claim 1 or claim 2, in which the polymer comprises polyurethane.

23. A method according to claim 22, in which the polyurethane is a linear segmented poly(ether)urethane with a number average molecular weight in the region of 20 to 100 kDa.

24. A method according to claim 1 or claim 2, in which the solvent comprises N,N-Dimethylacetamide.

26. A method according to any one of the preceding claims, in which the product comprises a vascular prosthesis.

27. A method according to claim 26, in which the prosthesis comprises a graft adapted for use in a part of a vascular system comprising branches therein.

28. A method according to claim 27, in which the prosthesis comprises a graft adapted to replace that part of the aorta from which the coronary arteries exit.

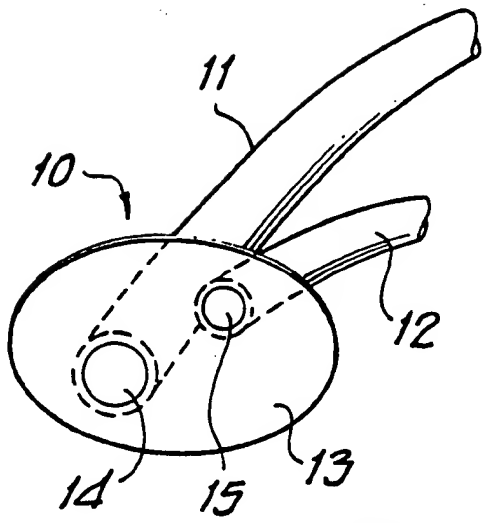

FIG.1

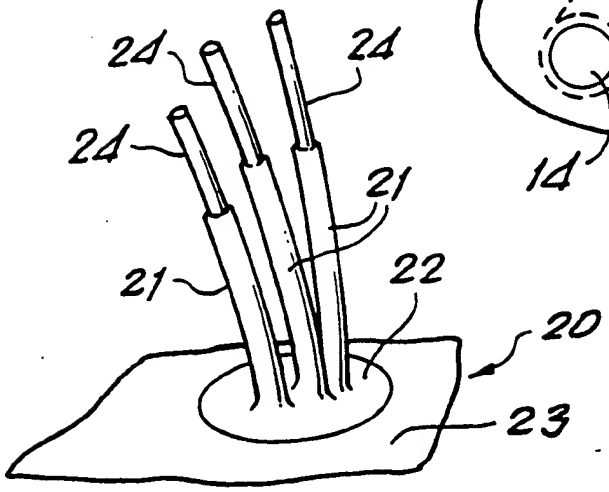

FIG.2

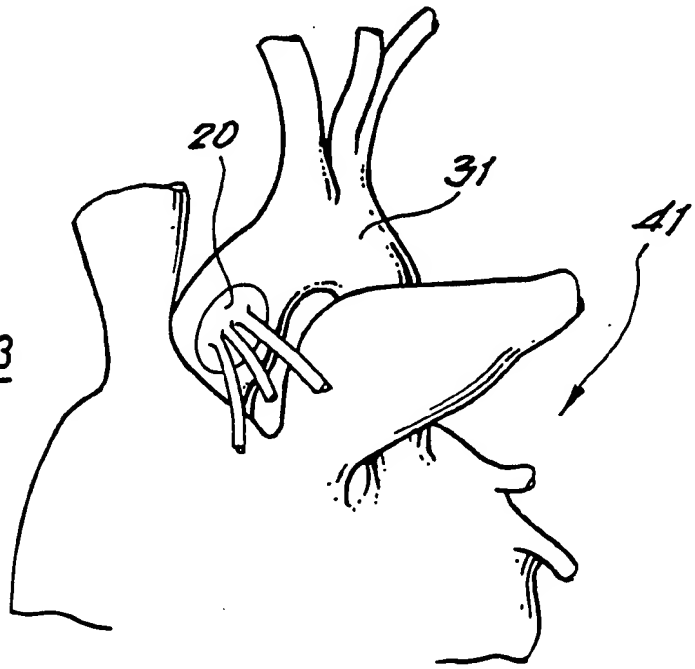

FIG.3

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/01591

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 F 2/04, A 61 L 27/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 F; A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with Indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP, A1, 0269254 (ETHICON INC) 1 June 1988, see column 6, line 2 - line 38; figure 2	1-2,6, 20,21, 26-28
X	US, A, 4605406 (CAHALAN ET AL) 12 August 1986, see the whole document	2-3,5-7, 12,20-23,26, 27
X	US, A, 4798607 (MIDDLETON ET AL) 17 January 1989, see column 4, line 58 - line 68	2,5-6, 22-24, 26

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21st January 1991	07. 02. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalia Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 4731073 (ROBINSON) 15 March 1988, see column 2, line 55 - line 62	2,6,22, 23,26

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

Claim 1 relates to a method of formming a polymer product from a vessel. Claim 2 relates to another method of formming a polymer product without formming a single general inventive concept (see PCT Rule 13.1).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. ☒ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 90/01591

SA 40981

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/12/90 The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A1- 0269254	01/06/88	AU-D-	8015087	28/04/88
		JP-A-	63158052	01/07/88
		US-A-	4883453	28/11/89
US-A- 4605406	12/08/86	AU-B-	573506	09/06/88
		AU-D-	4722085	07/03/86
		CA-A-	1244725	15/11/88
		EP-A-	0190283	13/08/86
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		WO-A-	86/01095	27/02/86
US-A- 4798607	17/01/89	DE-A-	3722111	21/01/88
		GB-A-	2192547	20/01/88
		JP-A-	63089165	20/04/88
		US-A-	4904272	27/02/90
US-A- 4731073	15/03/88	CA-A-	1207105	08/07/86
		DE-A-	3204719	16/09/82
		FR-A-B-	2499847	20/08/82
		GB-A-B-	2092894	25/08/82
		JP-A-	57150954	17/09/82
		US-A-	4604762	12/08/86